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Statement of C. Joseph Stetler, President
Pharmaceutical Manufacturers Association
Before the Health Subcommittee
of the
Senate Committee on Labor and Public Welfare

March 7, 1973

Mr. Chairman and Members of the Committee:

I am C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association. With me today are John G. Adams, Ph. D., PMA Vice President for Scientific and Professional Relations, and Bruce J. Brennan, PMA Vice President and General Counsel.

The Pharmaceutical Manufacturers Association is a trade association, whose 115 member firms conduct the bulk of the nation's research and development leading to the introduction of new prescription drugs. Currently, our members' efforts in this important work involve more than 20,000 research scientists and technicians, and the expenditure of more than $720 million annually.

It is our understanding that the Committee is interested today primarily in the use of volunteers in drug testing, and particularly in such testing among prisoners recruited for that purpose.

We welcome this opportunity to appear and commend your interest in drug research as it involves human volunteers and patients. Although the subject has been examined at length in the medical, legal and ethical communities, it is valuable for all of us to review it again in order to learn how well our efforts are working and how they can be further improved.

The need to test candidate compounds in human beings prior to broad scale marketing is obvious. Even the most extensive animal trials cannot be relied upon to predict the safety, mode of action, or the therapeutic effectiveness of any drug in man. Useful as animal data is, it provides only approximate indices of the safety of a new drug in man and affords only a general understanding of how the compound may be absorbed, metabolized, excreted and of its pharmacologic effects. When animal data is encouraging, we still arrive at an unavoidable point of fact: The proper vehicle for testing a drug's potential for man is man.

When sufficient animal data is accumulated, a notice of Investigational New Drug Exemption (IND) is submitted to the Food and Drug Administration. All of the known information about the drug is provided, and a detailed protocol is prepared, describing the planned trial in human subjects. That trial may not actually begin until the FDA has had thirty days to study the IND. If deemed necessary by the FDA, the study may be prohibited until data and satisfactory protocols are submitted.

In the majority of instances, though not in all, clinical trials begin in individuals who are not actually ill. With few exceptions, the tests in animals will also have involved animals which were free of disease.

It is important to understand that in these early studies of a candidate drug, safety, rather than efficacy, is being investigated. The compound would not be under investigation if there were not some demonstrated pharmacologic effect observed in animal studies, suggesting therapeutic efficacy for man. Nevertheless, the first human exposures to the drug are designed primarily to elucidate its general pharmacological and biochemical effects in man -- how it is absorbed,

at what rates, its possible site and mode of action, and its fate in the body. The dosages necessary to obtain this sort of information may be very low, so low in fact that they would not produce a therapeutic effect in patients.

These tests, referred to as Phase I trials, are restricted to very small numbers of human subjects. They may include single or multiple dose regimens over relatively short periods of time in order to obtain data on the overall pharmacological and biochemical characteristics of the compound. The experiments provide useful parameters on appropriate dosage levels, and indications as to the levels at which side effects might be expected to appear in patients.

Obviously, such information is of critical importance in designing trials involving the exposure of actual patients to the candidate drug.

One may understandably ask why these tests should not be conducted in patients, rather than in normal persons. In fact, sick individuals can be used in Phase I tests. For some drugs (the anti-cancer compounds are examples) the risks for the normal volunteer are too great. It is also generally agreed that, when the animal studies or other information have shown that the risk is such that the drug ought not be given to people who do not stand to benefit, it should be given its first human trials directly in patients. And there are other circumstances where it may be appropriate to use patients from the start, even where risk for normal subjects would not be a factor in itself.

However, these kinds of situations do not always prevail. Often, data from healthy subjects is invaluable in conducting responsible research. A normal subject's response to the drug often determines the best possible bases for proceeding.

Moreover, there are ethical and medical reasons for not doing the first human studies in the sick. First, available and effective or alternative therapy must be withdrawn from the patient in order to evaluate the safety of the experimental compound. Second, the dosages may be so low as to offer no possibility of therapeutic activity; or, they may be so high as to expose the diseased individual to a significant and hazardous added insult. Third, if side effects were to be observed in the sick patient, one would have difficulty determining whether these effects were due to the drug or were part of the disease process.

In all discussions about the use of normal individuals in drug testing programs, it is important to bear in mind that many of the medicines being investigated have already been used in man. This is because rising standards of science increasingly require that new studies be undertaken on established products so as to improve knowledge about the way they are metabolized, and to obtain additional bioavailability data.

Why Recruit Prisoners for Drug Testing?

The last fifteen years have witnessed a marked advance in the volume of medical research in this country, and, equally important, in the sophistication of that work. In drug research, it was commonplace only twenty years ago for reports to be based on more or less uncontrolled observations, where the study was less systematically designed, and where information on the pharmacological properties of the agent was sparse.

By the end of the 1950's, great progress had been achieved in the fields of clinical pharmacology, biopharmaceutics, medical instrumentation and biostatistics. The pharmaceutical industry, along with Federal and academic

research centers, made vital contributions to drug science. In a sense, the 1962 Amendments to the Food, Drug, and Cosmetic Act gave these developments official sanction. They instituted the requirement that carefully controlled human experimentation, based upon statistically valid designs, be conducted as a matter of routine. Henceforth, the law demanded, evidence in support of drug claims would in every case be generated out of factual documentation.

To do this kind of Phase I research properly, a number of conditions are desirable:

1. Relatively homogeneous subjects should be studies in order to facilitate the design of studies from which relatively precise conclusions could be reached in relatively little time.

2. The study group should be healthy for the reasons already mentioned. This allows the research team to study the effects of a carefully controlled escalation of dosage under close supervision, with maximum safety.

3. For the conclusions to be valid, only one variable -- the drug -- should be present. The study group, and the test environment (time, place, diet, exercise, etc.) should be held constant, insofar as that is possible.

4. Attention to detail must be explicit. Phase I studies in particular require many tedious and repetitive procedures, such as frequent blood urine, blood pressure, pulse and respiration tests.

These are not all of the prerequisites, but they are sufficient to demonstrate that the study group should be under regular observation, so that dosage routines, test procedures, reaction reports and consultation are carried out as planned -- needs that can seldom be met without recruiting institutionalized personnel. Prison inmates, students, and only a few other groups are logical

candidates for this kind of controlled study. And the accelerated (and accelerating) FDA demands for data have meant a parallel increase in the number of clinical investigations, particularly in prisons.

If it can be accepted that the use of prison inmates, or other institutionalized persons, is all but required in drug studies by present American standards of research, consideration must still be given to the motivations behind the prisoners' willingness to participate in these studies, to the manner in which they are conducted, to the protections afforded them, and to actions which should be considered for further improving the practice.

At the outset, we would point out that it is the prisoner's special situation as a healthy, institutionalized person, that qualifies him for recruitment for medical research -- not his social standing. His prisoner status itself should neither coerce nor prohibit his participation. He is most emphatically entitled to every protection and consideration given to any other member of society. The relatively recent public interest and concern for prison conditions and for the rights of the prisoner can be a major factor in ensuring that he is not exploited.

Why Do Prisoners Take Part in Drug Research?

While it is unquestionably essential to provide prisoners who join in drug studies with the same information and levels of protection that all others enjoy, we should also recognize that there are unique benefits which prisoners gain from taking part in these programs.

There seems to be general agreement that either the most, or one of the most, important factors behind prisoner participation in test projects is financial reward. Therefore, the rewards should not be disproportionate within

the context of prison life. Realistically, this means that compensation is usually at a rate that may seem to many to be unfairly low. In general, however, the fees are structured so as to avoid any financial coercion that might occur if drug testing were unusually rewarding relative to pay rates for other prison work. Except in rare instances, the amount the prisoner receives is decided by prison officials and not by the sponsors of the research.

Significant as the financial incentive is, it would be a mistake to conclude that it is the only motivation. Studies have shown that prisoners have additional reasons for participating. Many hope to escape the tediousness of prison life; to be part of a commendable effort; to show themselves and others that they can do good and worthwhile things; to gain acknowledgement as individuals deserving respect; to show authorities that they are reforming. Many are merely seeking a purpose or involvement to escape boredom.

Records show that prisoners rarely break rules or have disciplinary problems while in the testing programs. Volunteers are plentiful and while they are always free to leave the project, they rarely do so, apparently feeling that their role is useful which, of course, it is. Our feeling is that these experiences are of significant value to the prisoners, and that we should not deny willing prisoners the opportunities, so long as their health and their civil liberties are protected.

Informed Consent and the Prisoner

Granted that drug testing in normal human beings is scientifically valid and that half or more of such tests are done in prisons, one must recognize that there are differences between prisoner volunteers and others. Perhaps the most fundamental difference revolves around the question of freedom and the capability to give informed consent to an investigator.

There is no categorical answer to the informed consent problem, as anyone who has studied the matter knows. Perhaps the view of Dr. L. Alexander, writing in the Annals of the New York Academy of Science in 1970, can speak for most of those who have devoted many years to this subject:

> "The use of prisoners as research subjects poses special problems. While prisoners have collaborated effectively, safely, and without violation of their human rights or dignity in many important research studies such as Goldberger's famous pellagra experiments and many others, it may nevertheless be doubted whether any consent given by a prisoner, who by definition is restricted in his choices, could ever be regarded as truly voluntary. This question cannot be answered in a generally applicable manner, since the answer depends on the specific conditions, atmosphere, and morale in the particular prison involved. But I am certainly of the opinion that, in the absence of coercion and duress other than the fact of confinement per se and if no promise is made or implied that the condition of his confinement will be changed as a result of his participation in an experiment, a prisoner may make a valid voluntary decision to devote his time and energies to a project for the good of humanity, rather than to relatively meaningless tasks."

The process by which genuinely informed consent may be obtained is the subject of FDA regulations, which state in part that:

> " 'Consent' means that the person involved has legal capacity to give consent, is so situated as to be able to exercise free power of choice, and is provided with a fair explanation of pertinent information concerning the investigational drug, and/or his possible use as a control, as to enable him to make a decision on his willingness to receive said investigational drug. This latter element means that before the acceptance of an affirmative decision by such person the investigator should carefully consider and make known to him (taking into consideration such person's well-being and his ability to understand) the nature, expected duration, and purpose of the administration of said investigational drug; the method and means by which it is to be administered; the hazards involved; the existence of alternative forms of therapy, if any; and the beneficial effects upon his health or person that may possibly come from the administration of the investigational drug."

Clearly the wording of the FDA regulation explicitly reflects the objectives expressed in the Nuremburg Code and the Declaration of Helsinki, as well as the concepts expressed in the HEW Institutional Guide on the protection of human rights. Wording, which is accepted and applied by the pharmaceutical industry in the conduct of its research.

How Drug Tests Are Conducted in Prisons

Now, let me describe the procedures followed in prison tests sponsored by pharmaceutical houses. I should point out that of necessity my description will be general, reflecting what we understand to be the typical practice. As you know, situations vary widely; some firms operate and staff their own facilities within the prison, some maintain prison wards in general hospitals, others sponsor research conducted by individual investigators, and still others employ institutional contractors.

Test projects in prisons, like all clinical trials, must be the subject of investigational new drug exemptions (IND's) filed with the FDA. The IND gives complete details on the purpose and methodology to be employed, describes the number and characteristics of the subjects, and the qualifications of the investigator. Additionally, when institutionalized patients are involved, a local review committee must be empanelled, and its membership must be of varied background, including clergymen or other laymen, as well as scientists. The investigator must assure the sponsoring company and the FDA that the research program will not be started without the review committee's approval.

The basis for the clinical study is the protocol, which is a matter of extensive discussion and consideration before the study is initiated. The sponsoring firm determines that the institution where the research is to be conducted has adequate facilities, personnel and laboratories. Before final agreement, the investigator must accept the protocol and the conditions of the investigation. He is made aware of the pertinent regulations governing investigations, including consent procedures, adverse reaction reporting rules, and other requirements.

The researcher is given toxicologic and pharmacologic data on the drug he will be studying, as well as other meaningful facts. Throughout the course of the study, communication with the investigator is maintained at appropriate intervals, by mail, telephone or on-site visits.

No prisoner is started on the project until he has had a physical examination and is advised as to the nature of the study and the risks that are involved. The information is recorded on the consent form which is read to him, and which he studies and may ask questions about, before signing. He is told that he may withdraw from the study at any time, and that fact is stipulated on the consent form.

What Are Alternatives to the Use of Prison Volunteers?

If, as a society, we were to decide that prisoners were to be exempted from the right to take part in drug testing, even under the best of conditions, we must consider the available alternatives.

They are admittedly very few. If adopted, they could amount to a retreat from what we have learned about the value of normal human pharmacology studies in the past twenty years; they could severely limit the amount of data gathered prior to taking a candidate compound into large-scale clinical trials with sick people. Such a course is probably unacceptable to anyone aware of the scientific concessions involved and the resulting reductions in consumer protection.

We could attempt, of course, to do all Phase I trials in hospitals and clinics. That option, it seems to us, carries serious negative implications for medical and ethical reasons. Invariably the persons involved in such testing would be the underprivileged or the poor occupying the charity wards in hospitals.

Then, too, they are in various stages of illness and could not be considered normal healthy subjects.

A final alternative would be to limit the testing of any drugs to patients who are suffering from the disease the drug is designed to treat. As already noted, such a course would present major ethical and scientific pitfalls.

All things considered, Mr. Chairman, it seems that there are not sufficient reasons to deny prisoners, and others, the opportunity to participate in research programs, so long as that participation is decided freely and is conducted in accord with the highest standards of ethics and science. If we can agree that those standards are essentially adequate, and enforceable, and if we can agree that prisoners' rights to equality may include the right to aid science, then we need not spend time looking for ways to do away with prison testing. We can, instead, look for ways to further improve protections for the people involved in testing, whether in or out of prison. The pharmaceutical industry is anxious to be a part of that effort.

Observations and Recommendations

Out of our experience with prisoners, a number of general observations emerge. Certainly, one cannot review the subject without realizing that the general prison environment is involved. For example, prisoners volunteer so that they can get more medical attention, more human comforts, and more physical safety while they are involved in medical research projects. Some would certainly contend that such incentives should not exist. But, nevertheless, they do.

Similarly, the matter of compensation for taking part in research projects deserves more study. As indicated earlier, the compensation provided usually is deliberately held to a modest level by prison authorities, in part to avoid making participation too attractive. Yet the number of prisoners who volunteer for these projects is consistently greater than the number actually needed. For some inmates, participation in these studies constitutes the best and sometimes the only way to earn money at a socially acceptable task. In some cases, it may be the first financially rewarding and responsible project the man has ever encountered.

The pharmaceutical industry, through drug testing programs, is definitely involved in prisoners' lives, and that involvement, we believe, has to be productive for prisoners and for society in general. We acknowledge an obligation to do what we can to improve still further the manner in which testing is performed in correctional institutions. Errors and injuries have doubtless occurred, but they are rare by comparison to the number of prisoners who have successfully taken part in the studies.

In recent days, we have contacted the leadership of the National Council on Crime and Delinquency in order to gain that organization's advice and assistance in formulating possible improvements. We have discussed the convening of a broad cross-section of experts in medicine, industry, penology and public policy to discuss the subject in detail. One outcome of such a meeting might be a special set of guidelines for the protection of prisoners' rights in medical research. I have every confidence that we can, as an industry, work constructively with such a body to better serve the interests of prisoners who help to make advances in drug therapy available for us all.

At the moment, we believe that legislative action in this area is not indicated. We have, however, noted with interest the introduction of bills S. 878 and S. 974, 93rd Congress. We believe that such approaches merit broad support and approval.

I hope that our comments have been responsive to the Committee's area of interest. We will be happy to attempt to answer your questions.